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Zyprexa

- General
  - Generic name is olanzapine
  - Introduced 1996
- Evidence of safety and efficacy
  - General
    - Effective in adult and pediatric schizophrenia
    - May be useful in augmenting antidepressant efficacy in the treatment of depressive disorders.
    - May be useful in the treatment of behavior problems in autism and attention deficit-hyperactivity disorder.
    - FDA-approval
      - Mania and mixed episodes (monotherapy and adjunctive) in 2000; later for same in youth
      - Maintenance treatment of bipolar disorder in adults 2004
      - Zyprexa-Prozac combination (Symbyax) approved for bipolar I depression in 2003
      - May soon be approved as monotherapy for bipolar depression
      - Agitation (in intramuscular form)
      - Schizophrenia in adults; later for same in youth
        - Many studies
          - McEvoy et al, 2007: 52-week DB, RCT Zyprexa vs. Seroquel vs. Risperdal in early psychosis—comparable efficacy and overall tolerability
          - Zyprexa vs Geodon in a 28-week double-blind study in 277 patients with schizophrenia
            - Zyprexa was more effective
            - Geodon demonstrated less weight gain and less lipid profile difficulties
    - Adults
      - Mania
        - RCT comparing Zyprexa to lithium; manufacturer-sponsored; Zyprexa with 87% response rate vs 73% with lithium; no difference on depressive symptoms; weight gain more with Zyprexa (4 lbs vs. 1.6 lbs)
        - 6 studies demonstrating efficacy (Tohen; Tohen; Tohen; Tohen; Shi; Zakecka) in addition to below
        - A three and a four-week placebo-controlled, RCT in adults with mania:
          - 49-65% response rate with Zyprexa
          - 24-43% with placebo
        - Baldessarini, 2003: placebo-controlled, randomized, double-blind trials of Zyprexa in mania in adults, including rapid cycling—safe and effective
      - Bipolar depression
        - Increasing evidence, but more evidence for Symbyax (Zyprexa plus Prozac)
        - Symbyax
          - NNT 4 for response, 5 for remission
            - NNH 6 for wgt gain, 12 for sedation; also: diarrhea
          - Detke et al, 2015, Symbyax in children and adolescents with bipolar I depression
            - Significantly more effective than placebo
            - Side effects
              - Weight gain 20% Symbyax vs. 1.2% placebo
              - Appetite increase 16.5% Symbyax vs. 1.2% placebo
              - Headache 15.9% Symbyax vs. 14.1% placebo
              - Somnolence 15.9% Symbyax vs. 2.4% placebo
              - Tremor 8.8% Symbyax vs. 1.2% placebo
              - Inc in TG's 7.1% Symbyax vs. 2.4% placebo
              - Fatigue 6.5% Symbyax vs. 7.1% placebo
              - Vomiting 6.5% Symbyax vs. 7.1% placebo

        - Sedation 6.5% Symbyax vs. 0% placebo
    - Zyprexa (unapproved)
        - NNT 12 for response
            - NNH 6 for clinically significant weight gain and 7 for sedation
        - Wang et al, 2014; bipolar I depression
            - 8 weeks Zyprexa up to 20 mg/day (avg dose 14) vs. placebo
            - Improvement better with Zyprexa; evident by first week
            - By week 8, scores improved by 14 points with Zyprexa vs. 7 with placebo
            - After 8 weeks, 50% response rate with Zyprexa vs. 21% with placebo
            - After 8 weeks, 35% remission rate with Zyprexa vs. 12% with placebo
            - Side effects
                - Dry mouth
                - Headache
                - Increased appetite/weight (gained an average of 7 pounds (vs. 0 with placebo)
                - Adverse changes in glucose, cholesterol, and triglycerides
- Bipolar maintenance
    - Reduction in rate of relapse of mania and depression in bipolar disorder
    - Tohen, 2006: Zyprexa vs. placebo, 351 patients, adult bipolar disorder, up to 48 weeks:
        - 174 days to symptomatic relapse with Zyprexa (8-fold longer than placebo)
        - 22 days with placebo
    - Tohen, 2005: Zyprexa vs. lithium in maintenance treatment of adult bipolar disorder; 12 month; randomized, double-blind, controlled; 431 patients
        - Zyprexa was more effective than lithium in preventing mania or mixed episodes
        - Both equally effective in preventing depressive episodes.
        - Manic/mixed relapse:
            - 21-23.9% for Zyprexa
            - 26.4-33.3% for lithium depending on illness stage
- Evidence of efficacy as monotherapy for rapid cycling.
- Evidence of efficacy in preventing post-partum relapse
- Mixed episodes
    - Houston et al, 2006: Zyprexa added to lithium or Depakote → significant reduction in suicidal ideation by 1 week, as well as reductions in agitation, depression, somatic discomfort, and psychotic features
- Treatment-resistant depression
    - Thase et al, 2007: patients with treatment-resistant depression and who failed treatment with Prozac were then treated with Zyprexa and Prozac vs. Prozac alone (longer trial) vs. Zyprexa alone. Those taking Zyprexa and Prozac demonstrated significantly greater improvement than Zyprexa or Prozac alone; side effects of the Zyprexa and Prozac combination included:
        - Weight gain 35% vs. 6.8% Prozac alone vs. 39.7% Zyprexa alone
        - Increased appetite 32% vs. 5.8% Prozac alone vs. 30.7% Zyprexa alone
        - Dry mouth 28.5% vs. 8.7% Prozac alone vs. 31.7% Zyprexa alone
        - Somnolence 17.5% vs. 5.3% Prozac alone vs. 12.1% Zyprexa alone
        - Fatigue 14% vs. 7.8% Prozac alone vs. 14.1% Zyprexa alone
        - Headache 12.5% vs. 19.4% Prozac alone vs. 13.1% Zyprexa alone
        - Peripheral swelling 12% vs. 1% Prozac alone vs. 7.5% Zyprexa alone
        - Hypersomnia 10.5% vs. 2.4% Prozac alone vs. 11.1% Zyprexa alone
        - Tremor 10.5% vs. 8.7% Prozac alone vs. 8% Zyprexa alone
    - Shelton et al, 2006: clients with treatment-resistant (to one medication) unipolar depression, non-psychotic, 28 patients, treated with Prozac up to 60 mg/day; those that did NOT improve by 30% or more were then randomized to the following for 8 weeks:
        - Zyprexa 12.5 mg/day mean plus placebo—INITIAL benefit but relapsed within 3 weeks; 25% remission
        - Prozac continuation, ~52 mg/day mean—NO additional benefit; 20% remission
        - Zyprexa 13.5/day plus 52 mg/day Prozac—POSITIVE efficacy throughout the trial; 60% remission
    - Corya et al: positive
- Borderline personality disorder

- Zanarini et al, 2011: 5-10 mg/day effectivel mean wgt gain 6-7 pounds
- PTSD
  - 7 of 9 RCT's (Risperdal, Zyprexa) showed benefit (though small studies, other meds allowed)
  - Meta-analysis of 7 RCT, DB studies of Risperdal or Zyprexa either alone or as adjuvants positive (though only 192 patients involved in the studies)
  - Bartzokis et al 2005; Krystal et al 2011;
  - BUT, benefits were modest at best such that the risk-benefit ratio weighs towards recommendations against the use of Risperdal and atypical antipsychotic medications as monotherapy OR adjunctive treatment.
- Generalized anxiety disorder
  - Augmentation of SSRI treatment
    - Response rate improved from ~7.5% to 55% (Pollack et al, 2006)

- Youth
  - Mania
    - Tohen et al, 2007: 3 week double-blind, placebo contolled study of 161 youth with acute manic or mixed manic episodes, average age 15 (range 13.9-16.1 yo), modal dose 9.7 mg (range 5.2-14.2 mg)
      - Zyprexa more effective than placebo
      - Weight gain of 7% or more of baseline body weight 41.9% with Zyprexa and 1.9% with placebo
    - Joshi et al, 2006; treatment of mania in youth with bipolar disorder with and without OCD; 52 youth, average age 8.4 (range 5.3-11.5 yo); average dose 8.5 mg (range 4.2-12.8 mg):
      - Bipolar + OCD (20 youth)
        - Less response to Zyprexa (with about ½ less symptom reduction)
      - Bipolar without OCD (32 youth)
        - Double the reduction in symptoms vs. bipolar + OCD
    - RCT, DB study, 159 youth, effective in mania
    - Frazier et al, 2001: 8-week, open-label, monotherapy, 2.5-20 mg/day, 23 youth aged 5-14 yo
      - 74% response
      - 30% remission
      - 5-16 pound weight gain
  - Bipolar depression
    - Eli Lilly, Symbyax vs placebo
      - Symbyax 78.2% response vs. 59.2% with placebo
      - Symbyax 59% remission vs. 43.4 with placebo
      - 8-9 pound average weight gain
  - Bipolar maintenance
    - An open-label study in pediatric bipolar disorder showed evidence of efficacy in the treatment of pediatric bipolar disorder (but not in co-morbid ADHD symptoms).
    - Biederman et al, 2006: youth aged 4-6 with bipolar disorder, 8 week, open-label trial of Risperdal (16 youth) and Zyprexa (15 youth); results:
      - Drop-out rates:
        - 6% with Risperdal,
        - 40% with Zyprexa
      - Response rates:
        - 69% with Risperdal
        - 53% with Zyprexa
        - Reduction in symptoms greater with Risperdal
        - Reduction in symptoms was within one week of starting Risperdal and within two weeks
        - Depressive symptoms reduced with Risperdal but not Zyprexa
    - Chang and Ketter, 2000: Zyprexa at 2.5-5 mg/day as adjunctive in three acutely manic prepubertal children also treated with mood stabilizers; marked improvement evident in 3-5 days
    - Soutullo et al, 1999: seven adolescents with acute mania—safe and effective
  - Disruptive behavior disorders
    - Handen et al, 2006: disruptive behavior disorder and subaverage IQ; 16 youth, 13-17 yo; ~13.7 mg/day average; effective; 12.7 pound average weight gain

        - Masi et al, 2006: conduct disorder; chart review; 23 youth, 11-17 yo; 60% response rate
        - Stephens et al, 2004: tics and aggression; 10 youth, 7-13 yo; effective
    - Schizophrenia
        - Kryzhanovskaya et al, 2006: 6-week, double blind, RCT with placebo, in 107 adolescents, mean age 16.1 yo (range 13-17 yo), Zyprexa 2.5-20 mg/day (average 11.1 mg/day) vs. placebo—safe and effective though formal response rates 37.5% vs. 25.7% on placebo; weight gain 8-10 pounds vs. ~.22 pounds on placebo.
        - Sikich, 2006: 50 youth aged 8-19 with psychotic disorders randomly assigned to Zyprexa, Risperdal or Haldol, 8 weeks; at week 8, 27/50 responded and continued for an additional 12 weeks; few patients gained additional benefits in the latter 12 weeks (though the early benefit was maintain.
        - Kumra, 2006: 12-week randomized and double-blind comparison of Zyprexa and Clozaril in early-onset schizophrenia
            - 33% on Zyprexa experienced significant improvement
            - 66% on Clozaril
        - Beasley, 2003: Recent evidence in efficacy for delaying relapse of psychosis.
        - Mozes, 2003: children with drug-resistant schizophrenia, open label, 12-week trial, safe and effective
        - Ross, 2003: 20 children, open label, 1 year of treatment, safe and effective
        - Findling, 2002: 16 adolescents (~12 yo), open-label study, safe and efficacious
        - Frazier, 2001: open trial in pediatric bipolar disorder, 23 children, 8 weeks; safe and effective (61% response rate).
        - Grothe, 2000: 8 youths, looked at pharmacokinetics
        - Kumra, 1998: 8 youths, open-label study, vs. Clozaril, Clozaril better
        - Mandoki, 1997: 8 youths, chart review, all tolerated switch from Clozaril to Zyprexa
    - Autism spectrum disorder
        - Hollander et al, 2006; 11 kids (9 yo), 8 wk, double-blind, placebo-controlled, 8-12 mg/day
            - 50% response rate with Zyprexa
            - 20% response rate with placebo
- Some of the side effects and risks include:
    - Sleepiness/sedation13-60.7
        - 13% with 10 mg/day
        - 31.5% (Perlis et al, 2006)
        - 40% with 15 mg/day
        - 45.5% (JCP, 2006)
        - 60.7% with 15 mg/day if consider sedation, somnolence AND fatigue vs. 15% placebo
        - Provigil 100-200 mg/day may help.
    - Increased appetite/weight gain 29-47.3%
        - 29% or more of patients may gain more than 7% of their body weight in 6 weeks
        - 30.3% (13.9% increased appetite and 16.4% increased weight) (Perlis, 2006)
        - 47.3% in other studies
        - 12 pounds is the average
        - 24 pounds on 15 mg/day
        - weight gain tends to plateau after six months.
    - Lassitude (physically run down) in 29%
    - Dry mouth 7.5-28.5%, the latter percentage in Perlis, 2006
    - Dizziness 6.5-9%
    - Constipation and dry mouth in 5-10% of patients
    - Orthostatic hypotension
    - Glucose intolerance/diabetes
    - Cholesterol and lipid abnormalities
    - Increase in prolactin (usually transient)
    - Liver abnormalities (case reports)
        - 2% with significant elevations in liver enzymes
        - 5% or more with minor elevations
    - Slight increase in risk of seizures
    - Some muscle/motor; akathisia (muscle restlessness) in 5-10%

        - propanolol 10 mg 2-3 times-a-day may help (but could worsen othostatic hypotension).
    - Two cases of death associated with intramuscular injections of Zyprexa (being investigated, 2013)
    - A number of other side effects and risks in multiple organ systems.
    - Pregnancy
        - To date, not associated with congenital anomalies
        - Case studies and registries, both retrospective (23 patients) and prospective (69 patients), show no increase in the risk of major malformations (Goldstein et al, 200; McKenna, 2005)
        - Goldstein, 2000: 23 cases of prenatal use; no increased risk
- Pharmacodynamics, +
    - Effective range 2.5-20 mg/D
    - Comes in 2.5, 5, 7.5, 10, 15 and 20 mg tabs; also available is an 5 and 10 mg orally disintegrating tabs. Don't break either tab
    - Metabolized by **1A2 and 2D6 and UGT 1A4**
    - Half-life 30 hours (21-54 hours)
    - Peak level in 4.9 hours;
    - Blocks D1/2/3/4, 5HT2a/2c/3/6, muscarinic 1, histamine 1, alpha 1 receptors
- Zyprexa increases indices of new neuronal growth in the ventral medial prefrontal cortex; responders show greater increases than non-responders
- Symbyax (combination of olanzapine-fluoxetine)
    - FDA-approved for bipolar depression and the maintenance treatment of bipolar disorder.
    - Keck, 2005: treatment emergent mania 6.7 % of folks on placebo, 6.4% on Symbyax, and 5.7% on Zyprexa alone.
    - Comes in 6 mg O/25 mg F, 6 mg O/50 mg F, 12 mg O/25 mg F, and 12 mg O/50 mg F capsules.

A 52-Week Study of Olanzapine with a Randomized Behavioral Weight Counseling Intervention in Adolescents with Schizophrenia or Bipolar I Disorder

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OBJECTIVES: To evaluate the 52-week safety/tolerability of oral olanzapine for adolescents with schizophrenia or bipolar mania and compare effectiveness of a standard versus intense behavioral weight intervention in mitigating risk of weight gain.

METHODS: Patients 13-17 years old with schizophrenia (Brief Psychiatric Rating Scale for Children [BPRS-C] total score >30; item score ≥3 for hallucinations, delusions, or peculiar fantasies) or bipolar I disorder (manic or mixed episode; Young Mania Rating Scale [YMRS] total score ≥15) received open-label olanzapine (2.5-20mg/day) and were randomized to standard (n=102; a single weight counseling session) or intense (n=101; weight counseling at each study visit) weight intervention. The primary outcome measure was mean change in body mass index (BMI) from baseline to 52 weeks using mixed-model repeated measures. Symptomatology was also assessed.

RESULTS: No statistically significant differences between groups were observed in mean baseline-to-52-week change in BMI (standard: +3.6kg/m(2); intense: +2.8kg/m(2); p=0.150) or weight (standard: +12.1kg; intense: +9.6kg; p=0.148). Percentage of patients at endpoint who had gained ≥15% of their baseline weight was 40% for the standard group and 31% for the intense group (p=0.187). Safety/tolerability results were generally consistent with those of previous olanzapine studies in adolescents, with the most notable exception being the finding of a mean decrease in prolactin. On symptomatology measures, patients with schizophrenia had a mean baseline-to-52-week change in BPRS-C of -32.5 (standard deviation [SD]=10.8), and patients with bipolar disorder had a mean change in YMRS of -16.7 (SD=8.9), with clinically and statistically significant improvement starting at 3-4 days for each.

CONCLUSIONS: Long-term weight gain was high in both groups, with no statistically significant differences between the standard or intense behavioral weight interventions in BMI or weight. Safety, tolerability, and effectiveness findings were generally consistent with the known profile of olanzapine in adolescents.

The US Food and Drug Administration (FDA) is warning that the antipsychotic olanzapine (multiple brands) has been linked to a severe condition known as drug reaction with eosinophilia and systemic symptoms (DRESS).

The FDA Adverse Event Reporting System (FAERS) database identified 23 cases of DRESS reported with olanzapine worldwide since 1996, when the first olanzapine-containing product was approved.

In a release, the FDA notes that FAERS includes only reports submitted to the agency, so there are likely to be additional cases of which the FDA is unaware.

It reports that one patient taking olanzapine experienced DRESS and died; however, this patient was taking multiple medicines that could have contributed to death.

DRESS may start as a rash that can spread to all parts of the body. It can include fever, swollen lymph nodes, and a swollen face. It causes a higher-than-normal eosinophil count that can cause inflammation or swelling. DRESS can result in injury to organs, including the liver, kidneys, lungs, heart, or pancreas, and can lead to death. DRESS is a potentially fatal drug reaction with a mortality rate of up to 10%.

The FDA recommends that physicians immediately stop treatment with olanzapine if DRESS is suspected. There is currently no specific treatment for DRESS. The important ways to manage DRESS are early recognition of the syndrome, discontinuation of the offending agent as soon as possible, and supportive care.

Treatment with systemic corticosteroids should be considered in cases with extensive organ involvement. When prescribing the medicine, physicians should explain the signs and symptoms of severe skin reactions to their patients and should tell them when to seek immediate medical care.

Olanzapine Versus Risperidone in Children and Adolescents with Psychosis: A Meta-Analysis of Randomized Controlled Trials

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OBJECTIVE: To compare the efficacy and safety of olanzapine and risperidone in children and adolescents (aged ≤18 years) with psychosis by conducting a meta-analysis of randomized controlled trials (RCTs).
METHODS: Several English and Chinese databases were searched for studies published before February 8th, 2017. Two independent investigators screened the studies according to prespecified criteria and extracted the data. Review Manager 5.3 was used to conduct the data synthesis.
RESULTS: Eight RCTs involving 457 participants (225 participants in the olanzapine group and 232 participants in the risperidone group) were included. No significant differences were observed in the mean scores on the Positive and Negative Syndrome Scale/Brief Psychiatric Rating Scale (standard mean difference [SMD] = -0.06, 95% confidence intervals [CI] = [-0.31, 0.19], p = 0.63), the positive symptom scores (SMD = -0.09, 95% CI = [-0.32, 0.15], p = 0.48), or the negative symptom scores (SMD = -0.11 95% CI = [-0.34, 0.13], p = 0.38) between the two groups. Regarding adverse effects, the mean increases in weight (MD = 2.90, 95% CI = [1.41, 4.39], p = 0.0001), body mass index (MD = 0.90, 95% CI = [0.42, 1.38], p = 0.0003), and incidence of hypersomnia (risk ratios [RR] = 1.98, 95% CI = [1.15, 3.43], p = 0.01) were higher in the olanzapine group, while the incidence of insomnia (RR = 0.31, 95% CI = [0.11, 0.85], p = 0.02), prolactin elevation (RR = 0.11, 95% CI = [0.01, 0.85], p = 0.03), myotonia (RR = 0.12, 95% CI = [0.03, 0.49], p = 0.003), tremor (RR = 0.22, 95% CI = [0.08, 0.63], p = 0.005), and akathisia (RR = 0.27, 95% CI = [0.12, 0.57], p = 0.0007) was higher in the risperidone group.
CONCLUSIONS: There is no significant difference in efficacy between olanzapine and risperidone for the treatment of children and adolescents with psychosis, but the side effect profiles of these two medications differ. High-quality RCTs are needed before recommending clinical treatment in children and adolescents.